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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,188	02/16/2001	Mark Tuszynski	041673/2045	5329

30542 7590 09/08/2003

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/788,188	Tuszynski et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *3-14-03 and 3-27-03*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above, claim(s) *11-25* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7 & 12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-10 and SEQ ID No. 2, in Paper Nos. 13 and 16 is acknowledged. The traversal is on the ground(s) that SEQ ID Nos. 2, 4, 6 and 8 represent related proteins having same N-glycosylation sequence and same kind of mutation in that sequence and they are not "unrelated and diverse". Applicants further argue that 1996 examination guideline provides up to 10 such sequence to be examined. This is not found persuasive because SEQ ID Nos. 2, 4, 6 and 8 represent different and distinct DNA sequences derived from different genes. Although they have same N-glycosylation sequence and same kind of mutation in that sequence, they represent amino acid sequences of different genes. The chemical structures, physical properties, and biological functions of those genes and their gene products, i.e. proteins, all differ and are distinct from each other. Further, the examination guideline has been changing since 1996 and examiner is not bound to the 1996 examination guideline. Thus, the SEQ ID Nos. 2, 4, 6 and 8 are patentably distinct from each other and require separate search.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 11-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper Nos. 13 and 16.

Applicants' preliminary amendment filed 3-14-03 has been entered. Claim 9 has been amended. Claims 1-25 are pending and claims 1-10 and SEQ ID No. 2 are considered.

Claim Objections

3. The claim page (specification, page 15) should start with "I claim", "We claim", or "What is claimed is" but **not** "Claim". Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "at a position 8 amino acids upstream from the site of cleavage for the mature growth factor" in claim 1 is vague and renders the claim indefinite. It is unclear what defines the "site of cleavage for the mature growth factor" and what is considered a "site of cleavage for the mature growth factor". The specification fails to specifically define "site of cleavage for the mature growth factor". Claims 2-4 depends on claim 1 but fail to clarify the indefiniteness.

The phrase "at a position 4 amino acids upstream from the site of cleavage for the mature growth factor" in claim 5 is vague and renders the claim indefinite. It is unclear what defines the "site of cleavage for the mature growth factor" and what is considered a "site of cleavage for the mature growth factor". The specification fails to specifically define "site of cleavage for the mature growth factor". Claims 6-8 and 10 depend on claim 5 but fail to clarify the indefiniteness.

Claim 9 is vague and indefinite because it is unclear whether the claimed mutant pro-neurotrophin comprises or consists of or consists essentially of SEQ ID Nos. 2, 4, 6 or 8.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-8 and 10 read on a mutant pro-neurotrophin having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature growth factor substituted with a basic residue, such as serine. The specification discloses wild type human NGF, BDNF, NT-3 and NT-4/5 amino acid sequences (SEQ ID Nos. 1, 3, 5, 7) and mutant pro-neurotrophin amino acid sequences of human NGF, BDNF, NT-3 and NT-4/5 (SEQ ID Nos. 2, 4, 6, 8). SEQ ID Nos. 2, 4 and 6 have asparagine at a position 8 amino acids upstream of cleavage site of mature growth factor substituted with serine and SEQ ID No. 8 has asparagine at a position 5 **(not 4)** amino acids upstream of cleavage site of mature growth factor substituted with serine.

The family of neurotrophin includes NGF, BDNF, NT-3, NT-4/5, NT-6, CNTF, GDNF, LIF, TGF, FGFs 1-15, BMPs, IGF-1, PDGF and EGF etc. (See specification, pages 1-2). NGF includes alpha-NGF, beta-NGF and gamma-NGF. The claims encompass any mutant pro-neurotrophin of various members of neurotrophin family derived from numerous different organisms, such as humans, mice, rats, bovines, ovines, bids, other mammals, fishes, and insects etc. The specification fails to provide sufficient description for the cleavage site of numerous mature neurotrophin family members and whether either at a position 8 amino acids or 4 amino acids upstream of said cleavage site would be an asparagine that can be substituted with a basic residues, such as serine. Although the claims limit the mutated position to 8 or 4 amino acids upstream of cleavage site, however, the scope of the claimed mutant neurotrophin is very broad and there is the lack of description of the cleavage site of various different neurotrophin family members. The genus of various pro-neurotrophin mutant is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of the cleavage site of various different neurotrophin family members and their upstream amino acid sequences. The specification also fails to provide sufficient description for whether there is an asparagine residue at a position 4 amino acids upstream of the cleavage site of numerous mature neurotrophin family members.

This limited information disclosed by the present application is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed

mutant pro-neurotrophin proteins. Thus, it is concluded that the written description requirement is not satisfied for the mutant pro-neurotrophin proteins as claimed.

8. Claims 1-8 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the amino acid sequence comprising SEQ ID No. 2, does not reasonably provide enablement for any mutant pro-neurotrophin having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature growth factor substituted with a basic residue, such as serine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-8 and 10 are directed to a mutant pro-neurotrophin having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature growth factor substituted with a basic residue, such as serine. Claims 2 and 6 specify the basic residue is serine.

The specification discloses wild type human NGF, BDNF, NT-3 and NT-4/5 amino acid sequences (SEQ ID Nos. 1, 3, 5, 7) and mutant pro-neurotrophin amino acid sequences of human NGF, BDNF, NT-3 and NT-4/5 (SEQ ID Nos. 2, 4, 6, 8). SEQ ID Nos. 2, 4 and 6 have asparagine at a position 8 amino acids upstream of cleavage site of mature growth factor substituted with serine and SEQ ID No. 8 has asparagine at a position 5 **(not 4)** amino acids upstream of cleavage site of mature growth factor substituted with serine.

The family of neurotrophin includes NGF, BDNF, NT-3, NT-4/5, NT-6, CNTF, GDNF, LIF, TGF, FGFs 1-15, BMPs, IGF-1, PDGF and EGF etc. (See specification, pages 1-2). NGF includes alpha-NGF, beta-NGF and gamma-NGF. The claims encompass any mutant pro-neurotrophin of various members of neurotrophin family derived from numerous different organisms, such as humans, mice, rats, bovines, ovines, bids, other mammals, fishes, and insects etc.

As discussed above under 35 U.S.C. 112 first paragraph written description rejection, the limited information disclosed by the present application is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed mutant pro-neurotrophin proteins. Thus, one skilled in the art at the time of the invention would not know how to use the claimed mutant neurotrophin proteins. The specification fails to provide adequate guidance and evidence for whether a mutant neurotrophin protein, other than SEQ ID No. 2, having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature growth factor substituted with a basic residue, such as serine, would have improved secretion efficiency from host cells than wild-type neurotrophin. The specification also fails to provide the structural features of the cleavage site of various different neurotrophin family members and their upstream amino acid sequences. It should be noted that the amino acid residue at a position 4 amino acids upstream of the cleavage site of NT4/5 is arginine (R) not asparagine (N). The specification fails to provide adequate guidance and evidence for whether substitution of the amino acid residues at a position 4 amino acids upstream

of the cleavage site of any neurotrophin family member with a basic residues, such as serine, would result in mutant pro-neurotrophin having improved secretion efficiency from host cells than wild-type neurotrophin.

The specification states that "Despite many of their structural similarities, nervous system growth factors act on discrete and different targets. Little is known about which amino acid residues within a growth factor are necessary to its activity...as little as the first 9 residues of the N-terminus and the last two residues from the C-terminal of purified recombinant human NGF produces a neurotrophin molecule which is 300-fold less efficient in binding activity as compared to wild-type hNGF" (specification, p. 3, lines 5-11). Further, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the

multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2).

In view of the scope of the claimed invention, the lack of structural features of the cleavage site of the mature growth factor and its upstream amino acid sequence, and the unpredictability of protein function from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the claimed mutant neurotrophin proteins.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working example provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.